Patent
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:	)	
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Avraham COHEN et al.	)	Group Art Unit: 1625
	)	
Application No.: 10/507,485	)	Examiner: Margaret M. Seaman
	)	
Filed: September 13, 2004	)	Confirmation No.: 8571
	)	
For: ENANTIOMER (-) OF TENATOPROZOLE AND THE THERAPEUTIC USES THEREOF	)	

DECLARATION OF GEORGE SACHS PURSUANT 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, George Sachs, declare as follows:

1. I reside at 17986 Boris Drive Encino, CA 91316.

2. I am a citizen of the United States of America.

3. My educational background is as follows:

University of Edinburgh	1957	B.Sc., Biochemistry
University of Edinburgh	1960	M.B., Ch.B., Medicine
University of Edinburgh	1980	D.Sc. Biochemistry
University of Gothenburg	1987	M.D., Medicine

4. I am a Professor of Medicine and Physiology, Wilshire Chair in Medicine, and Director of Membrane Biology Lab at the University of California, Los Angeles and a Staff Physician at the Los Angeles VA Greater LA Healthcare System. I have been employed by the University of California, Los Angeles since 1982.

5. I have served on the Center for Ulcer Research and Education Executive Committee and Advisory Board since 1982 and I have been the director and co-director of the Center for Ulcer Research and Education.

6. I am a named author on more than three hundred (300) journal publications (peer-reviewed), more than sixty (60) published reviews, six (6) text books, seven (7) letters, and three (3) editorials.

7. My research interests are in the field of gastroenterology and the microbiology of *H. pylori*. Specifically, my research interests include membrane transport processes, pump mechanisms, epithelial cell function, and bacterial bioenergetics.

8. A copy of my complete Curriculum Vitae is attached as Exhibit A.

9. I am not an inventor of U.S. Patent Application Serial No. 10/507,485. However, I am familiar with the patent application, as well as the experimental data that has been generated with regard to the metabolism of tenatoprazole (namely, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]imidazo[4,5-b]pyridine), including the racemate, the R-enantiomer (the (+) enantiomer), and the S-enantiomer (the (-) enantiomer).

Background

10. Proton pump inhibitors (PPIs) are usually used for treating various acid-related diseases of the upper gastro-intestinal tract, especially gastro-oesophageal reflux disease (GERD). After accumulation at the level of the gastric parietal cell and after chemical rearrangement, proton pump inhibitors bind covalently to the enzyme responsible for the transport of protons into the gastric juice, and hence, irreversibly inhibit gastric acid secretion.

Tenatoprazole

11. Tenatoprazole is the result of research aimed at prolonging the plasma half-life (*i.e.*, residence time in the blood) of PPIs, through manipulations of the benzimidazole structure. Tenatoprazole is an imidazopyridine derivative, with an increased plasma half-life in humans.

12. The clinical development of the tenatoprazole racemic mixture has demonstrated the clinical significance of the long half-life. The inhibition of acid secretion caused by tenatoprazole was sustained throughout the night and thus, has resulted in earlier efficacy and relief in patients with GERD. Studies have provided evidence of non-proportionality between the augmentation of pharmacokinetic parameters and the increase in dose of racemic tenatoprazole. A high inter-subject variability of the pharmacokinetics and of the pharmacodynamic response (level of acid inhibition) has been seen. For example, one subject presented a six-fold increase in the exposure (*i.e.*, the area under the plasma concentrations/time curve (AUC)).

13. This observation triggered the implementation of a specific study to identify the human cytochromes involved in the metabolism of tenatoprazole racemate, the (+) enantiomer, and the (-) enantiomer.

In vitro Identification of Cytochromes involved in (+) and (-) Enantiomer Metabolism

14. An *in vitro* study of cytochromes involved in the metabolism of the (+) enantiomer and the (-) enantiomer of tenatoprazole (TU-199) was performed. I have reviewed the results of this study in detail. Data from the study is attached as Exhibit B.

15. The results of the *in vitro* metabolism study identified the human cytochromes involved in the metabolism of the (+) enantiomer and the (-) enantiomer of tenatoprazole, using cDNA-expressed human CYPs. It was determined that CYP 2C19 is involved in 80 % of the metabolism of (+) enantiomer of tenatoprazole. For the (-) enantiomer, it was determined that CYP 2C19 was involved in only 53.4 % of the metabolism, and importantly, it was identified that CYP 3A4 was involved in 27.3 % of the metabolism and CYP 2C9 was involved in 19.3 % of the metabolism of this enantiomer.

16. Accordingly, CYP 2C19 is the dominant pathway for the metabolism of the (+) enantiomer of tenatoprazole. In contrast, pathways other than CYP 2C19 exist for metabolism of the (-) enantiomer (*i.e.*, CYP 3A4 and CYP 2C9).

17. Subjects with a genetic deficiency of the CYP 2C19 pathway (so called "poor metabolizers") account for the observed high inter-subject variability of the pharmacokinetics and of the pharmacodynamic response (level of acid inhibition) when dosing with the tenatoprazole racemate and the (+) enantiomer. These "poor metabolizers" have increased half-life and exposure (*i.e.*, the area under the plasma concentrations/time curve (AUC)), raising potential safety concerns.

18. In contrast, the (-) enantiomer has "escape" metabolic pathways in subjects with a genetic deficiency of the CYP 2C19 pathway (*i.e.*, CYP 3A4 and CYP 2C9). Therefore, even these "poor metabolizer" subjects can metabolize the (-) enantiomer. As such, the (-) enantiomer

exhibits a predictable half-life and exposure even in these "poor metabolizers" and therefore, can be dosed more safely and predictably in all subjects.

19. The incidence of so-called "poor metabolizers" is about 3 % in Caucasians and over 20 % in Asians and 6% in Hispanics.

Study of single and repeated oral administration of tenatoprazole racemate and enantiomers

20. A double blind, placebo controlled study on the tolerability of single and repeated dosing of tenatoprazole racemate (TU-199), as well as the (+) and (-) enantiomers, in healthy males was performed. I have reviewed the results of this study in detail. Data from the study is attached as Exhibit B.

21. In this study, the tenatoprazole racemate (TU-199), as well as the (+) and (-) enantiomers of tenatoprazole, were administered to sets of eight subjects per dose. The drug was administered once per day on day 1 of the study (the single administration phase) and then administration was resumed at once per day on days 14-20 (the repeated administration phase). C_{max} (maximum concentrations), T_{max} (maxiumum time), AUC (area under the curve) and $t_{1/2}$ (half-life) were determined for the racemate, as well as the (+) and (-) enantiomer. Values for "poor metabolizers" were not included in this data.

22. In the data in attached Exhibit B, it is seen that the pharmacokinetics of the racemate are not linear, and it is seen that the pharmacokinetics of the (+) enantiomer also are not linear. However, it is surprisingly seen that the pharmacokinetics of the (-) enantiomer are linear. Since the pharmacokinetics of the (-) enantiomer are linear, the non-linearity of the tenatoprazole racemate is due specifically to the (+) enantiomer.

23. The non-linear profile of the (+) enantiomer and the racemate result in unpredictability and reduction in safety in dosing in all patients since there is no proportionality between the increase in dose and increase in plasma concentrations. In contrast, the (-) enantiomer exhibits a linear profile providing predictability in dosing in all patients and increased safety since there is proportionality between the increase in dose and increase in plasma concentrations.

24. The metabolic by-products of the (+) enantiomer exhibit an inhibitory effect on the metabolism of the (+) enantiomer. This data further shows that the (+) enantiomer, and the racemate, are unpredictable in patient dosing.

Study of pharmacokinetics of tenatoprazole racemate and enantiomers in extensive and poor metabolizers

25. An open-label parallel-group study on the pharmacokinetics of the tenatoprazole racemate (TU-199), the (+) enantiomer, and the (-) enantiomer after single oral dose administration in extensive and poor CYP2C19 metabolizers was performed. I have reviewed the results of this study in detail. Data from the study is attached as Exhibit B. The "extensive metabolizers" do not have the genetic deficiency of the CYP 2C19 pathway and are considered "normal" subjects.

26. In this study, the tenatoprazole racemate (TU-199), as well as the (+) and (-) enantiomers of tenatoprazole, were administered to eight healthy volunteers (four poor metabolizers and four extensive metabolizers). The volunteers were given a single 20 mg oral dose under fasting conditions. The study period was 192 hours after administration for the poor metabolizers and 72 hours after administration for the extensive metabolizers. The C_{max}, T_{max}, AUC and $t_{1/2}$ of TU-199 (+) enantiomer, and (-) enantiomer were determined.

27. When comparing the C_{max}, T_{max}, AUC and $t_{1/2}$ for the racemate and the (+) enantiomer for the poor metabolizers and the extensive metabolizers, drastic differences are observed. However,

for the poor metabolizers and the extensive metabolizers, unexpectedly, there is no significant pharmacokinetic variation in the C_{max}, T_{max}, AUC and $t_{1/2}$ for the (-) enantiomer.

28. The mean exposure (AUC) to tenatoprazole racemate (TU-199) was found to be over four-fold higher in poor metabolizers in comparison to extensive metabolizers. The elimination half-life ($t_{1/2}$) of the tenatoprazole racemate (TU-199) was about 30 hours in poor metabolizers, compared to 6 hours in extensive metabolizers.

29. Unexpectedly, this difference is due to the (+) enantiomer. The mean exposure (AUC) to the (+) enantiomer was found to be over 21-fold higher in the same poor metabolizers in comparison to the same extensive metabolizers (*i.e.*, 173,996 ng/h/mL^{-1} vs. 8,085 ng/h/mL^{-1}). In addition, the half-life ($t_{1/2}$) was increased by eight-fold (36.7 vs. 4.5 hours).

30. In contrast, the (-) enantiomer showed only a slightly increased half-life in the same poor metabolizers in comparison to the same extensive metabolizers (*i.e.*, 9.7 vs. 5.7 hours).

Conclusions

31. Unexpectedly, the pharmacokinetics of (-) enantiomer are linear in both subjects without a genetic deficiency of the CYP 2C19 pathway ("normal subjects") and in subjects with a genetic deficiency of the CYP 2C19 pathway ("poor metabolizers"). The linearity allows for predictability in dosing in all patients, thus providing increased safety in dosing in all patients.

32. Also unexpectedly, the pharmacokinetics of (+) enantiomer are not linear in either subjects without a genetic deficiency of the CYP 2C19 pathway ("normal subjects") or in subjects with a genetic deficiency of the CYP 2C19 pathway ("poor metabolizers"). The metabolic by-products of the (+) enantiomer exhibit an inhibitory effect on the metabolism of the (+) enantiomer. Possible safety concerns arise from the poor predictability in dosing in all

patients, the increased half life and exposure in patients, and the increased potential for drug interactions.

33. In summary, the (-) enantiomer has a predictable pharmacodynamic response, due to its linear pharmacokinetic response to dosing. The racemate and the (+) enantiomer are not predictable in this way. The (-) enantiomer showed a lower variability in metabolism in both subjects without a genetic deficiency of the CYP 2C19 pathway ("normal subjects") or in subjects with a genetic deficiency of the CYP 2C19 pathway ("poor metabolizers"). Therefore, the (-) enantiomer could be administered to any subject, without considering the subject's CYP 2C19 polymorphism status.

34. Moreover, it is my opinion that it is unexpected that the (-) enantiomer of tenatoprazole exhibits such a different pharmacokinetic profile, in comparison to the tenatoprazole racemate and the (+) enantiomer.

I further declare that all statements made herein of my own knowledge are true and that all statements on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 10/26/05

George Sachs

CURRICULUM VITAE

PERSONAL HISTORY:

NAME: George Sachs

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BIRTHDATE: August 26, 1935

PLACE OF BIRTH: Vienna, Austria

CITIZENSHIP: U.S.A.

EDUCATION:

University of Edinburgh	1957	B.Sc., first class honors	Biochemistry
University of Edinburgh	1960	M.B., Ch.B., with honors	Medicine
University of Edinburgh	1980	D.Sc.	Biochemistry
University of Gothenburg	1987	M.D., (Hon Causa)	Medicine

LICENSURE: California, Physician and Surgeon #A 54208

PROFESSIONAL EXPERIENCE:

PRESENT POSITIONS:

University of California, Los Angeles	1982-present	Professor, Medicine & Physiology
University of California, Los Angeles	1982-present	Wilshire Chair in Medicine
University of California, Los Angeles	1987-present	Director, Membrane Biology Laboratory
VAGLAHS-West Los Angeles	1999-present	Staff Physician

PREVIOUS POSITIONS:

Albert Einstein College	1961-1962	Instructor
Columbia University	1962-1963	Research Associate

University of Alabama in Birmingham	1963-1965	Assistant Professor, Medicine & Physiology
University of Alabama in Birmingham	1965-1970	Associate Professor, Medicine & Physiology
University of Alabama in Birmingham	1970-1982	Prof. Medicine & Physiology
University of Alabama in Birmingham	1974-1982	Director, Membrane Biology
University of Alabama in Birmingham	1979-1982	Professor, Medicine & Physiology & Biophysics
University of California, Los Angeles	1982-1987	Director, Center for Ulcer Research & Education
VAGLAHS-West Los Angeles	1984-1999	Senior Medical Investigator
University of California, Los Angeles	1987-2003	Co-Director, Center for Ulcer Research & Education

PROFESSIONAL ACTIVITIES:

COMMITTEE SERVICES:

National:
National Committee Biophysical Society, 1976-1978
NSF Panel for Metabolic Biology, 1977-1979
American Physiological Society GI Steering Committee, 1977-1981
NIH Study Section, Physiology, 1979-1983
National Board Medical Examiners, 1979-1983
VA Merit Review Board, 1984-1987
National Committee Biophysical Society, 1987-1989
NIAMS, Board of Scientific Counselors, NIH, 1993
NIH Study Section NIDDK Digestive Disease Centers, 2000-Present
NIH Advisory Board, 2002
NIH Study Section NIDDK Digestive Disease Centers, 2002-Present
NIH Special Study Section, 2003-Present

Local:
Center for Ulcer Research and Education Executive Committee, 1982-Present
Center for Ulcer Research and Education Advisory Board, 1982-Present
Veterans Administration Review Committee, 1983-1986
IBD/Harbor UCLA Advisory Board, 1988-1992
Chair, Academic Personnel Committee, UCLA, 1990-1991
GI/UCLA Search Committee, 1992-1993
UCLA Specialty Training and Academic Research Committee (STAR), 1993-1995
UCLA, Academic Personnel ad hoc Review Committee, 1994
VAMC, Wadsworth, ACOS for Research Search Committee, 1994
VAMC, West Los Angeles R&D, GI and Hepatic Disorder Review Group, 1996
VAMC, West Los Angeles Merit Review Committee, 1996
VAMC, West Los Angeles Internal Merit Review Committee, 1996
VAGLAHS-West Los Angeles, Chair, Research Sub-Committee, 2000-Present

PROFESSIONAL ASSOCIATIONS:

American Gastroenterological Association
American Physiological Society

American Society for Biochemistry and Molecular Biology
American Society of Biological Chemistry
American Society for Microbiology
American Society of Renal Biochemistry and Metabolism
Biochemical Society
British Gastroenterological Association (Honorary)
Society of General Physiology

EDITORIAL SERVICES:

American Journal of Physiology, Editorial Board, 1968-1977
American Journal of Physiology, Associate Editor, 1977-1985
Hypertension, Editorial Board, 1982-1985
Physiological Reviews, Editorial Board, 1983-1989
Annual Review of Physiology, Associate Editor, 1985-1990
American Journal of Physiology, Editorial Board, 1985-Present
American Heart Association, Review Board, 1988-1991
Alimentary Pharmacology & Therapeutics, Editorial Board, 1988-2004
Digestive Diseases and Sciences, Editorial Board, 1990-Present
Frontiers of Bioscience, Editorial Board, 2001
World Journal of Gastroenterology, Editorial Board, 2004-Present
Reviewer, Biochemistry, 2004-Present

HONORS AND SPECIAL AWARDS RECEIVED:

Humboldt Award for U.S. Senior Scientists, 1973-1974
Hoffman LaRoche Award, 1982
Senior Medical Investigatorship, Veterans Administration, 1984-1999
Beaumont Prize in Gastroenterology, American Gastroenterological Association, 1985
Middleton Award, Veterans Administration, 1992
"Ismar Boas Vorlesung" Medal, German Gastroenterological Association, 1992
Fifth "Morton I. Grossman Distinguished Lectureship", 1993
Honorary Membership, British Society of Gastroenterology, 1993
Distinguished Lecturer, Department of Pharmacology, University Texas Medical School at Houston, 1995
Outstanding Scientific and Technical Award, Federal Executive Board of Los Angeles, 1996
Honorary Degree, Doctor of Medicine, Medical Faculty of Gothenburg University, Sweden, 1996
Horace W. Davenport Distinguished Lecturer of the APS Gastrointestinal Section, 1998
Janssen Award for Special Achievement in Gastroenterology, 1998
Outstanding Scientific and Technical Award, Federal Executive Board of Los Angeles, 1998
Outstanding Supporter, Upward Bound Internship Program Harvey Mudd College, 2000
Gairdner Foundation Awardee, 2004
Dr. Norman Frankel Scholar to the University of Chicago, 2005

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Journal Publications (Peer-Reviewed):

1. G. Sachs and O. Braun-Falco. The occurrence and nature of arylsulfatases in parakeratoses. *J.Invest Dermatol.* 34:439-444, 1960.
2. G. Sachs, C. Deduve, B. S. Dvorkin, and A. White. Effect of adrenal cortical steroid injection on lysosmal enzymic activities of rat thymus. *Exp.Cell Res.* 28:597-600, 1962.
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7. G. Sachs, R. Shoemaker, and B. I. Hirschowitz. Action of 2-deoxy-D-glucose on frog gastric mucosa. *Am.J.Physiol* 209 (3):461-466, 1965.
8. G. Sachs, W. E. Mitch, and B. I. Hirschowitz. Frog gastric mucosal ATPase. *Proc.Soc.Exp.Biol.Med.* 119 (4):1023-1027, 1965.
9. B. I. Hirschowitz and G. Sachs. Reversal of insulin inhibition of gastric secretion by intravenous injection of potassium. *Am.J.Dig.Dis.* 11 (3):217-230, 1966.
10. G. C. Luketic, G. Sachs, J. Myren, T. Tsuji, and B. I. Hirschowitz. Effects of colchicine on intestinal mucosal dehydrogenases. II. Biochemical observations. *Am.J.Dig.Dis.* 11 (5):404-409, 1966.
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12. G. Sachs, R. L. Shoemaker, and B. L. Hirschowitz. Effects of sodium removal on acid secretion by the frog gastric mucosa. *Proc.Soc.Exp.Biol.Med.* 123 (1):47-52, 1966.
13. R. L. Shoemaker, G. Sachs, and B. I. Hirschowitz. Secretion by guinea pig gastric mucosa in vitro. *Proc.Soc.Exp.Biol.Med.* 123 (3):824-827, 1966.
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15. B. I. Hirschowitz and G. Sachs. Insulin effects on gastric secretion and blood electrolytes modified by injected potassium. *Am.J.Dig.Dis.* 12 (1):7-18, 1967.
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ments of serum iron, folate, and vitamin B_{12}. Iron or folate deficiency should be treated by oral replacement. Vitamin B_{12} deficiency should be treated with monthly intramuscular injections of the vitamin.

OSTEOMALACIA AND OSTEOPOROSIS Osteoporosis and osteomalacia are common after partial or complete gastrectomy but occur rarely after vagotomy with pyloroplasty. Osteomalacia is extremely frequent following gastrojejunostomy or Billroth II anastomosis. These bone changes are believed to result from malabsorption of calcium and vitamin D. Patients may develop bone pain and have pathologic fractures. The incidence of bone fractures in men following gastric resection has been estimated to be almost twice that of control subjects of similar age. Reduced bone density identified by x-ray requires years to develop. Patients with osteomalacia usually have increased levels of serum alkaline phosphatase and may have reduced serum calcium concentrations. These patients should be treated by supplemental oral vitamin D and calcium. The frequency of osteoporosis and osteomalacia after partial or complete gastrectomy is sufficiently great to justify treatment with vitamin D and calcium indefinitely, especially in females, following gastric resection.

GENERAL MALABSORPTION (See also Chap. 254) Mild, chemically demonstable steatorrhea is common in patients after ulcer surgery. Weight loss is more common after partial gastric resection (approximately 60 percent of patients) than with vagotomy without resection. The major cause of weight loss is reduced food intake. On a 100-g fat diet, loss of stool fat seldom exceeds 15 g/d (normal individuals less than 7 g/d). The causes of maldigestion and malabsorption after peptic ulcer surgery include rapid gastric emptying, reduced dispersion of food in the stomach, reduced bile concentrations in the gut lumen, increased rate of transit of the meal through the small intestine, and reduced or delayed pancreatic secretory responses to feeding. Steatorrhea and weight loss, sometimes accompanied by vitamin B_{12} malabsorption, may develop as a result of bacterial overgrowth, especially in patients with afferent loop bacterial stasis. Overt symptoms and other manifestations of malabsorption appearing after surgery for peptic ulcer also may be due to other preexisting conditions, including latent celiac sprue and chronic pancreatitis.

CARCINOMA AFTER PARTIAL GASTRECTOMY Several studies have documented an increased incidence of adenocarcinoma of the stomach in duodenal ulcer patients following partial gastric resection and after vagotomy and drainage without resection. This usually develops 10 or more years after ulcer surgery. The possibility of carcinoma of the stomach should be considered when abdominal symptoms, which may be similar to or distinct from those due to the original ulcer, appear many years after apparently successful surgery.

ZOLLINGER-ELLISON SYNDROME (GASTRINOMA)

In 1955, Zollinger and Ellison described the syndrome that bears their names, which consists of ulcer disease of the upper gastrointestinal tract, marked increases in gastric acid secretion, and non-beta islet cell tumors of the pancreas.

ETIOLOGY AND PATHOGENESIS Zollinger and Ellison, in their original description of the syndrome, suggested that the ulcer disease in these patients resulted from release of a secretagogue from these tumors into the circulation which accounted for the often enormously increased rates of gastric acid secretion. Their proposal proved correct when in 1960 extracts of Zollinger-Ellison (Z-E) tumors were shown to stimulate gastric acid secretion. Subsequently, it was found that these pancreatic islet cell tumors contained gastrin and that there were large amounts of this hormone in the circulation producing the pathophysiologic characteristics of the syndrome. These gastrin-containing tumors are therefore now called *gastrinomas*.

Gastrinomas have been reported most often within the pancreas. Pancreatic gastrinomas may vary in size from 1 mm to more than 20 cm in diameter. Multiple primary tumors are common. From one-half to two-thirds of patients have multiple gastrinomas. Pancreatic gastrinomas are most common in the head of the pancreas. In more than half of Zollinger-Ellison patients harboring gastrinomas the tumors cannot be identified at surgery. There is recent evidence that with careful search when gastrinomas are located they are found as frequently (or perhaps more frequently) in the wall of the duodenum as in the pancreas. Duodenal gastrinomas, approximately 50 percent of which are solitary, are usually found in the submucosa of the first or second parts of the duodenum. Gastrinomas also have been located less commonly in other sites, including the hilum of the spleen and rarely in the stomach. Gastrinomas have been found in lymph nodes in proximity to the pancreas, proximal duodenum, and spleen in the absence of demonstrated primary tumors. These probably represent local metastases from undiscovered duodenal wall gastrinomas. Approximately 90 percent of gastrinomas are found within an anatomic triangle (the gastrinoma triangle) which is comprised of the junction of the cystic and common bile ducts superiorly, the junction of the second and third portions of the duodenum inferiorly, and the junction of the pancreatic body and neck medially. In unusual instances, the Z-E syndrome has resulted from gastrinomas originating from remote organs, e.g., parathyroid and ovarian tumors. About two-thirds of gastrinomas are histologically or biologically malignant. Malignant gastrinomas usually grow slowly; however, a small portion may be rapidly invasive and may metastasize early and widely. Metastasis is most often to regional lymph nodes and liver; spread also may be to peritoneal surfaces, spleen, bone, skin, or mediastinum. Gastrinomas have light-microscopic similarities to carcinoid tumors and may be mistaken for these tumors, especially when gastrinomas arise from the mucosa of the small intestine or stomach. Pancreatic islet cell hyperplasia occurs in approximately 10 percent of patients with the Z-E syndrome. Hyperplasia of the islets, accompanying recognized or unidentified gastrinoma, appears to be an association or a consequence, rather than a cause, of excess gastrin release, since gastrin is not present in the hyperplastic tissue.

In an estimated 20 to 60 percent of patients with the Z-E syndrome the gastrinoma is a component of the multiple endocrine neoplasia type 1 (MEN 1) syndrome, an autosomal dominant disorder with a high degree of penetrance and great variability in expressivity. The MEN 1 locus is on chrosomome 11. Patients with MEN 1 may have clinically recognized hyperplasia, adenomas, or carcinoma involving, in order of frequency, the parathyroid glands, pancreatic islets, and pituitary. Hyperparathyroidism has been reported in 87 percent of patients with MEN 1 syndrome, and gastrinoma has been reported in approximately half of them (see Chap. 343). However, there is accumulating evidence that when carefully sought for there is probably involvement of all three organs in all patients with MEN 1, although it is frequently without overt clinical expression. Gastrinomas in non-MEN 1 patients are considered to be sporadic. Multiple gastrinomas are usually present in patients with MEN 1 and are usually smaller than sporadic gastrinomas. Gastrinomas with MEN 1 are located more frequently in the wall of the duodenum than in the pancreas. Patients, including those with duodenal gastrinomas, usually have multiple pancreatic islet cell tumors, most of which are not gastrinomas.

In most gastrinomas, approximately 80 to 95 percent of gastrin is in the form of heptadecapeptide gastrin (G-17), with most of the remainder being G-34. In contrast, approximately two-thirds of circulating gastrin in gastrinoma patients is G-34; most of the remainder is G-17. However, smaller amounts of even larger forms of gastrin and smaller gastrin fragments can be detected in the serum. When examined carefully, almost all gastrin-secreting islet cell tumors are found to contain multiple hormones that are usually clinically silent. These have included, among others, ACTH, glucagon, melanocyte-stimulating hormone, parathyroid hormone, growth hormone releasing factor (GRF), insulin, pancreatic polypeptide, and vasoactive intestinal peptide. Of these, ACTH is the most common; it is found in approximately 30 percent of gastrinomas. Cushing's syndrome with increased serum ACTH levels has been reported in 8 percent of 75 Z-E patients. ACTH-releasing gastrinomas are often aggressively malignant. In contrast, ACTH may be released by pituitary tumors in patients with MEN 1, in whom symptoms of Cushing's syndrome

are generally mild and gastrinomas are usually not metastatic. Approximately one-third of patients with gastrinomas have increases in serum concentrations of *pancreatic polypeptide*.

The parietal cell mass is substantially expanded to from three to six times normal secondary to the trophic effects of circulating gastrin on parietal cells. Small, multicentric, noninvasive carcinoid tumors have been identified in the gastric mucosa of patients with the Z-E syndrome. These tumors and associated focal areas of enterochromaffin-like (ECL) cell hyperplasia are believed to result from substantial and sustained hypergastrinemia. They also have been found in the gastric mucosa of patients with pernicious anemia and achlorhydria, who have striking increases in serum gastrin in the range of those found with gastrinoma.

While the true incidence of the Z-E syndrome is not known, estimates are that it accounts for 0.1 to 1 percent of peptic ulcers. The Z-E syndrome may occur at any age, but initial manifestations occur most commonly between the ages 30 and 60.

CLINICAL FEATURES From 90 to 95 percent of patients with gastrinomas develop ulceration of the gastrointestinal tract at some point during the course of their disease. Profound gastric acid hypersecretion is found in most, but not all, patients. Especially early in the course of the disease, symptoms are usually similar to those of patients with typical peptic ulcer. However, ulcer symptoms may be more fulminant, progressive, and persistent and, in general, respond poorly to usual medical and surgical peptic ulcer treatment programs. The anatomic site of the ulcers in patients with gastrinoma is similar, but not identical, to that of patients with common types of peptic ulcer. About 75 percent of gastrinoma patients have ulcers in the first portion of the duodenum or in the stomach; these are usually single but may be multiple. When multiple ulcers occur, they are frequently located not only in the first portion of the duodenum, the site of common duodenal ulcer, but also in the remainder of the duodenum or even the jejunum. In one large series, 14 percent of the ulcers were in the duodenum beyond its first portion and 11 percent in the jejunum.

Diarrhea occurs in about 40 percent of patients, and about 7 percent of patients with gastrinoma have diarrhea in the absence of ulcer disease. The diarrhea is due to the outpouring of large amounts of hydrochloric acid into the proximal duodenum and can be reduced or eliminated by aspiration of gastric juice. The excessive acid has been shown to reduce the pH of the contents of the proximal and distal jejunum to as low as 1 and 3.6, respectively. Inflammatory changes may be produced in the mucosa of the small intestine secondary to the injurious effect of large amounts of acid and pepsin. Steatorrhea, which is less common than diarrhea, results from inactivation of pancreatic lipase by large concentrations of acid in the proximal small intestine and from decreases in luminal bile acids. The decrease in intraluminal bile acid concentration is caused by precipitation of the major bile acids at low pH. This leads to impaired micelle formation, which, in turn, reduces intestinal absorption of fatty acids and monoglycerides (see Chap. 254). Vitamin B_{12} malabsorption, not correctable by addition of intrinsic factor, has been detected in some patients with the Z-E syndrome. Although gastric secretion of intrinsic factor appears normal, the reduced pH within the gut interferes with intrinsic factor–mediated vitamin B_{12} absorption. This can be corrected by neutralization of the intestinal contents. The mechanisms by which low pH in the gut interferes with intrinsic factor action is not known.

DIAGNOSIS The presence of gastrinoma should be suspected in patients with a compatible clinical history, especially in those with marked acid hypersecretion. More than 90 percent of gastrinoma patients have basal gastric acid outputs (BAO) that exceed 15 mmol/h. In some instances, the basal output may be greater than 150 mmol/h. However, there is substantial overlap in rates of gastric acid secretion among patients with gastrinoma, those with duodenal ulcer, and normal subjects. Gastrinoma patients often have BAO rates that are greater than 60 percent of those induced by maximal stimulation (MAO). In most normal subjects and duodenal ulcer patients, basal acid secretory rates are less than 60 percent of maximal secretion. However, because of frequent exceptions in patients with gastrinomas and common duodenal ulcers, the use of the BAO/MAO ratio is of no value in the certain identification of patients with gastrinoma.

Some radiographic features may suggest the diagnosis of the Z-E syndrome. Large mucosal folds may be demonstrated most prominently in the stomach but also in the duodenum and, in some instances, the jejunum. The lumen of the stomach and small intestine often contains large amounts of fluid. Radiographic features of most ulcers in these patients, except when they are distal in location, are similar to those of common peptic ulcer. Gastrinomas are difficult to localize. In almost half of patients with clinical and laboratory evidence, the tumors cannot be identified at surgery. Selective arteriography identifies gastrinomas in approximately one-third of patients with clinical and biochemical evidence of the Z-E syndrome. Computed tomography (CT) identifies gastrinomas in 30 percent and ultrasound in 15 percent of patients with the Z-E syndrome. Use of both selective arteriography and CT has been reported to identify 44 percent of gastrinomas in Z-E patients and 80 percent of those located at surgery. Endoscopic retrograde pancreaticoduodenography has not proved to be of assistance in the diagnosis or exclusion of pancreatic gastrinomas. A small number of duodenal wall gastrinomas have been identified and confirmed histologically by duodenoscopy.

The diagnosis in a patient with clinical features consistent with the Z-E syndrome depends on the demonstration of *increased serum gastrin levels* by radioimmunoassay. Fasting serum gastrin levels in normal subjects and patients with typical duodenal ulcer average approximately 20 to 50 pg/mL and usually do not exceed 150 pg/mL. Patients with gastrinoma almost always have fasting serum gastrin levels that are greater than 200 pg/mL and have been found as high as 450,000 pg/mL. Approximately half these patients have fasting serum gastrin levels that are less than 1000 pg/mL (an approximate mean value for serum gastrin for patients with gastrinoma).

Several provocative tests have been used to evaluate patients with possible gastrinoma, especially those who do not exhibit pronounced hypergastrinemia (i.e., serum gastrin > 1000 pg/mL). These tests utilize measurements of serum gastrin levels in response to intravenous secretin injection, calcium infusion, or ingestion of a standard test meal.

In the *secretin injection test*, secretin (Kabi secretin, 2 units per kilogram) is given intravenously over 30 to 60 s. Gastrin is measured in serum samples obtained immediately before injection of secretin, at 2 and 5 min after secretin, and at 5-min intervals thereafter for a total of 30 min. In normal individuals and patients with common duodenal ulcer, secretin produces no change, small reductions, or small increases in serum gastrin levels. In contrast, in gastrinoma patients, intravenous secretin induces substantial increases in serum gastrin. The serum gastrin levels increase promptly by at least 200 pg/mL, usually at 5 min (and virtually always by 10 min), and then gradually decrease toward or to preinjection levels by 30 min. In the *calcium infusion test*, serum samples for gastrin measurements are obtained before and at 30-min intervals for 4 h after initiation of a constant 3-h intravenous infusion of calcium gluconate (5 mg calcium per kilogram per hour). In gastrinoma patients, serum gastrin concentrations usually increase above the basal serum gastrin level by more than 400 pg/mL. The third provocative test involves the *feeding of a standard meal*: Gastrin is measured in serum samples obtained before the meal and at 15-min intervals after it for 90 min. This test has been used to attempt to distinguish between patients with gastrinoma and those with hypergastrinemia and gastric acid hypersecretion due to antral gastrin cell hypertrophy or hyperplasia.

The secretin injection test is by far the most valuable provocative test in identifying gastrinoma patients. Positive serum gastrin responses to intravenous secretin are found in more than 95 percent of patients with gastrinoma. Using the criteria suggested, substantial increases in serum gastrin following secretin injection have been detected only rarely in nongastrinoma patients. Reduced gastric acid

secretion, achlorhydria or profound hypochlorhydria, is by far the most common cause of hypergastrinemia. For this reason, gastric acid secretion should be measured before consideration of the secretin injection test. Exaggerated release of gastrin in response to calcium infusion is found in more than 80 percent of gastrinoma patients; however, this exaggerated response to calcium infusion occurs in some nongastrinoma patients with hypergastrinemia (e.g., with achlorhydria). Enhanced gastrin release with calcium infusion is rarely observed in gastrinoma patients in the absence of the abnormally large gastrin release in response to secretin. Since the calcium infusion test does not add significantly to the sensitivity or specificity of the secretin injection test, and since calcium infusion is potentially more hazardous, it is usually not necessary or recommended.

In a very small proportion of duodenal ulcer patients (much less than 1 percent), gastric acid hypersecretion may be accompanied by increased serum gastrin levels due to hyperfunction and/or hyperplasia of antral gastrin cells (G cells). These patients can be distinguished from those with gastrinoma by the secretin injection and meal stimulation tests. In patients with this antral gastrin cell abnormality, intravenous secretin does not produce large increases in serum gastrin characteristic of gastrinoma. Some authors have reported increases in serum gastrin concentrations greater than 200 percent after test meals in patients with gastrin cell hypertrophy or hyperplasia, suggesting that this may be of value distinguishing these patients from those with gastrinoma. Other authors more recently have found similarly large amounts of gastrin released into the sera of patients with gastrinomas, suggesting that the meal-stimulated test is of limited value in distinguishing between patients with antral gastrin cell hyperplasia and those with gastrinoma.

TREATMENT In general, patients with Z-E syndrome are resistant to those medical therapies and surgical procedures designed for and usually effective in treating common peptic ulcer. Antacids may produce transient symptom relief but rarely, if ever, induce ulcer healing or sustained relief of symptoms. Incomplete gastric resection (with or without vagotomy) or pyloroplasty with vagotomy is frequently followed by prompt and often fulminant ulcer recurrence. In the past, many patients with gastrinoma had multiple surgical procedures, particularly in those instances in which the diagnosis was not established initially. Mortality was reported to be lowest in patients with the Z-E syndrome in whom gastrectomy was the initial gastric surgery. This led to the conclusion that when surgery was required in gastrinoma patients, total gastrectomy was the surgical procedure of choice.

Development of effective drugs to reduce acid secretion and more precise diagnostic techniques to locate gastrinomas have increased substantially the therapeutic options. The key to management in these patients is individualization of treatment, since patients with the Z-E syndrome are highly heterogeneous with respect to clinical manifestations and extent of disease. As with many other predominantly malignant tumors, the ideal treatment is removal of the gastrinoma.

H-2 receptor antagonists are effective in reducing gastric acid secretion, producing symptom relief, and inducing ulcer healing in patients with the Z-E syndrome. *Cimetidine* was the first H-2 receptor antagonist used successfully in the treatment of these patients. Improvement in clinical symptoms, decreases in gastric acid output, and ulcer healing were found in 80 to 85 percent. Administration of cimetidine was required at 4- to 6-h intervals, with total daily doses usually four to eight times those used in the treatment of common duodenal ulcer. More recently, *ranitidine*, *famotidine*, and *nizatidine* also have been shown effective in treatment of patients with the Z-E syndrome. These H-2 receptor antagonists require comparable increases in dosage when compared with doses used in treatment of common duodenal ulcer. When instituted, H-2 receptor antagonist therapy must be continued indefinitely, since even temporary discontinuance is usually followed by ulcer recurrence. Ulcers fail to respond or recur while on treatment with H-2 receptor antagonists in approximately 25 percent of patients with the Z-E syndrome. The dose of H-2 receptor antagonist required to maintain a satisfactory reduction in gastric acid secretion can be assessed by measuring the basal gastric acid output during the hour immmediately prior to the next anticipated dose of the drug; the goal is to reduce gastric acid output to less than 10 mmol/h at that time.

Omeprazole, the parietal cell H^+,K^+-ATPase inhibitor, is the most effective drug and agent of choice in reducing gastric acid secretion and in healing ulcer in Z-E patients, including those with ulcers resistant to treatment with H-2 receptor antagonists. As a function of potency and dosage, the effectiveness of omeprazole can be prolonged and sustained. The usual initial daily recommended dose of omeprazole is 60 mg in a single dose administered in the morning before breakfast. The dose is adjusted to maintain gastric acid secretion to less than 10 mmol/h during the hour immediately before the next dose is due. Twice a day dosing is recommended if the patient requires 100 mg or more omeprazole per day. Some Z-E patients, in whom gastrinomas could not be identified or removed surgically, have been treated with parietal cell vagotomy, which has reduced or, in a few instances, eliminated the dose of H-2 receptor antagonist required in these patients.

Treatment for patients with the Z-E syndrome should be individualized. In selecting the best therapy, the biologic behavior of the tumor and the clinical manifestations in each patient must be taken into consideration. Early studies indicated that morbidity and mortality in patients with the Z-E syndrome were due principally to complications of severe ulcer disease. However, with earlier diagnosis, effective antiulcer treatment, and longer follow-up, more frequent consequences of the malignant properties of gastrinoma are now recognized. Approximately 50 percent of patients with the Z-E syndrome in whom the gastrinoma has not been removed will die from malignant invasion by the tumor. Complete *surgical resection of the tumors*, when possible, represents *optimal treatment in patients with gastrinoma*. Complete surgical removal of gastrinoma, with cure, has been achieved in approximately 25 percent of patients with the Z-E syndrome. Successful resection of tumor in Z-E patients with sporadic gastrinoma or with gastrinoma with MEN I requires thorough abdominal exploration and recognition and removal of multiple gastrinomas when found, including those in the wall of the duodenum and other extrapancreatic sites. Gastrinoma in lymph nodes and metastatic to the liver should be removed when safe and possible.

Treatment with omeprazole is indicated in the period during which the diagnosis is being established, while the location and extent of the tumor are being determined, and also as treatment prior to anticipated surgery. At present, omeprazole is certainly indicated for patients who are unsatisfactory candidates for surgery, in those who refuse surgery, and in those in whom surgical removal of the tumor is not possible. Patients with aggressively invasive gastrinoma have been treated with streptozotocin and 5-fluorouracil, in some instances combined with doxorubicin, in attempts to reduce tumor bulk and associated symptoms. Success with chemotherapy is limited, with only an initial response of approximately 40 percent and no complete responses. When metastatic and/or otherwise nonresectable gastrinoma is present, control of the ulcer disease may be achieved in most instances by treatment with omeprazole or, rarely, when required, by total gastric resection. There is no convincing evidence that tumor progression is usually influenced by gastrectomy.

STRESS ULCERS AND EROSIONS

A number of acute ulcerative lesions of the gastrointestinal tract are distinct clinically from chronic peptic ulcer. Among these are the acute upper gastrointestinal erosions and ulcers often observed in patients with shock, massive burns, sepsis, and severe trauma. These are often referred to as *stress erosions* and *ulcers*. These lesions, which are frequently multiple, are most common in the acid-secreting portion of the stomach, but they also may occur in the antrum and duodenum.

These erosions and superficial ulcers are extremely frequent and

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ncrease in cytosolic Ca^{2+}. Both pathways activate the H^+,K^+–ATPase (the proton pump). The H^+,K^+–ATPase consists of a large α-subunit and a smaller β-subunit. This pump generates the largest ion gradient known in vertebrates, with an intracellular pH of about 7.3 and an intracanalicular pH of about 0.8.

The most important structures in the central nervous system (CNS) involved in central stimulation of gastric acid secretion are the dorsal motor nucleus of the vagal nerve (DMNV), the hypothalamus, and the nucleus tractus solitarius (NTS). Efferent fibers originating in the DMNV descend to the stomach *via* the vagus nerve and synapse with ganglion cells of the enteric nervous system (ENS). ACh release from postganglionic vagal fibers can stimulate directly gastric acid secretion through a specific muscarinic cholinergic receptor subtype, M_3, located on the basolateral membrane of the parietal cells. The CNS probably modulates the activity of the ENS with ACh as its main regulatory neurotransmitter. The CNS generally is thought of as the main contributor to the initiation of gastric acid secretion in response to the sight, smell, taste, and anticipation of food ("cephalic phase"). ACh also indirectly affects the parietal cell through the stimulation of histamine release from the enterochromaffin-like (ECL) cells in the fundus and the stimulation of gastrin release from the G cells in the gastric antrum.

Histamine is released from ECL cells through multifactorial pathways and is a critical regulator of acid production through the H_2 subtype of receptor. ECL cells usually are found in close proximity to parietal cells. Histamine activates the parietal cell in a paracrine fashion; it diffuses from its release site to the parietal cell. Its involvement in gastric acid secretion (whether or not as the final, common, effector hormone) has been convincingly demonstrated by the inhibition of acid secretion with the use of H_2-receptor antagonists. The ECL cells are the sole source of gastric histamine involved in acid secretion.

Gastrin primarily is present in the antral G cells. As with histamine, the release of gastrin is regulated through multifactorial pathways involving, among other factors, central neural activation, local distention, and chemical components of the gastric content. Gastrin stimulates acid secretion predominantly in an indirect manner by causing the release of histamine from ECL cells; a less-important, direct effect of gastrin on parietal cells also is seen.

Somatostatin, localized in the antral D cells, may inhibit gastrin secretion in a paracrine matter, but its exact role in the inhibition of gastric acid secretion remains to be defined. There appears to be a decrease in D cells in patients with *Helicobacter pylori* infection, and this may lead to excess gastrin production due to a reduced inhibition by somatostatin.

Gastric Defense. The stomach protects itself from damage by gastric acid through several mechanisms such as the presence of intercellular tight junctions between the gastric epithelial cells, the presence of a mucin layer overlying the gastric epithelial cells, the presence of prostaglandins in the gastric mucosa, and secretion of bicarbonate ions into the mucin layer. Prostaglandins E_2 and I_2 inhibit gastric acid secretion by a direct effect on the parietal cell mediated by the EP_3 receptor (*see* section entitled "Prostaglandin Analogs," below). In addition, prostaglandins enhance mucosal blood flow and stimulate secretion of mucus and bicarbonate.

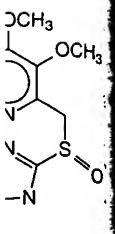
AGENTS USED FOR SUPPRESSION OF GASTRIC ACID PRODUCTION

Figure 37–1 provides the rationale and pharmacological basis for the classes of drugs currently used to combat acid-peptic diseases. The most commonly used agents at present are the proton pump inhibitors and the histamine H_2-receptor antagonists.

Proton Pump Inhibitors

Chemistry, Mechanism of Action, and Pharmacological Properties. The most effective suppressors of gastric acid secretion undoubtedly are the gastric H^+,K^+–ATPase (proton pump) inhibitors. They are the most effective drugs used in antiulcer therapy and have found worldwide popularity over the past decade. Currently, there are several different proton pump inhibitors available for clinical use: *omeprazole* (PRILOSEC), *lansoprazole* (PREVACID), *rabeprazole* (ACIPHEX), and *pantoprazole* (PROTONIX). They are α-pyridylmethylsulfinyl benzimidazoles with different substitutions on the pyridine or the benzimidazole groups; their pharmacological properties are similar. Proton pump inhibitors are "prodrugs," requiring activation in an acid environment. These agents enter the parietal cells from the blood and, because of their weak basic nature, accumulate in the acidic secretory canaliculi of the parietal cell, where they are activated by a proton-catalyzed process that results in the formation of a thiophilic sulfenamide or sulfenic acid (Figure 37–2). This activated form reacts by covalent binding with the sulfhydryl group of cysteines from the extracellular domain of the H^+,K^+–ATPase. Binding to cysteine 813, in particular, is essential for inhibition of acid production, which is irreversible for that pump molecule. Proton pump inhibitors have profound effects on acid production. When given in a sufficient dose (*e.g.*, 20 mg of omeprazole a day for seven days), the daily production of acid can be diminished by more than 95%. Secretion of acid resumes only after new molecules of the pump are inserted into the luminal membrane. Omeprazole also selectively inhibits gastric mucosal carbonic anhydrase, which may contribute to its acid suppressive properties.

Pharmacokinetics. Proton pump inhibitors are unstable at a low pH. The oral dosage forms ("delayed release") are supplied as enteric-coated granules encapsulated in a gelatin shell (omeprazole and lansoprazole) or as enteric-coated tablets (pantoprazole and rabeprazole). The granules dissolve only at an alkaline pH, thus preventing degradation of the drugs by acid in the esophagus and stomach. Proton pump inhibitors are rapidly



PRAZOLE

contraindications to oral ingestion, but this picture is expected to change with the advent of intravenous preparations of proton pump inhibitors. *Pantoprazole,* a relatively more acid-stable compound, is the first such preparation to be approved in the United States. A single intravenous bolus of 80 mg can inhibit acid production by 80% to 90% within an hour, an effect that can last up to 21 hours. Therefore, once-daily dosing of intravenous proton pump inhibitors (in doses similar to those used orally) may be sufficient to achieve the desired degree of hypochlorhydria. The clinical utility of these formulations in the above situations will require further study but is expected to be equal to if not greater than that of intravenous H_2-receptor antagonists.

The requirement for acid to activate these drugs within the parietal cells has several important consequences. The drugs should be taken with or before a meal, since food will stimulate acid production by parietal cells; conversely, coadministration of other acid-suppressing agents such as H_2-receptor antagonists may diminish the efficacy of proton pump inhibitors. Since not all pumps or all parietal cells are functional at the same time, it takes several doses of the drugs to result in maximal suppression of acid secretion. With once-a-day dosing, steady-state inhibition, affecting about 70% of pumps, may take 2 to 5 days (*see* Sachs, 2000). Achieving steady-state inhibition may be accelerated somewhat by more frequent dosing initially (*e.g.,* twice daily). Since the binding of the drugs' active metabolites to the pump is irreversible, inhibition of acid production will last for 24 to 48 hours or more, until new enzyme is synthesized. The duration of action of these drugs, therefore, is not directly related to their plasma half-lives.

Adverse Effects and Drug Interactions. Proton pump inhibitors inhibit the activity of some hepatic cytochrome P450 enzymes and therefore may decrease the clearance of benzodiazepines, warfarin, phenytoin, and many other drugs. When disulfiram is coadministered with a protein pump inhibitor, toxicity has been reported. Proton pump inhibitors usually cause few adverse effects; nausea, abdominal pain, constipation, flatulence, and diarrhea are the most common side effects. Subacute myopathy, arthralgias, headaches, and skin rashes also have been reported.

Chronic treatment with omeprazole decreases the absorption of vitamin B_{12}, but insufficient data exist to demonstrate whether or not this leads to a clinically relevant deficiency. Hypergastrinemia (>500 ng/liter) occurs in approximately 5% to 10% of long-term omeprazole users. Gastrin is a trophic factor for epithelial cells, and there is a theoretical concern that elevations in gastrin can promote the growth of different kinds of tumors in the gastrointestinal tract. In rats undergoing long-term administration of proton pump inhibitors, there has been development of enterochromaffin-like cell hyperplasia and gastric carcinoid tumors secondary to sustained hypergastrinemia; this has raised concerns about the possibility of similar complications in human beings. There are conflicting data on the risk and clinical implications of enterochromaffin-like cell hyperplasia in patients on long-term proton pump inhibitor therapy. These drugs now have a track record of more than 15 years of use worldwide, and no major new issues regarding safety have emerged (Klinkenberg-Knol *et al.,* 1994; Kuipers and Meuwissen, 2000). There is as yet no reason to believe, therefore, that hypergastrinemia should be a trigger for discontinuation of therapy or that gastrin levels should be monitored routinely in patients on long-term proton pump inhibitor therapy. However, the development of a hypergastrinemic state may predispose the patient to rebound hypersecretion of gastric acid following discontinuation of therapy.

Proton pump inhibitors have not been associated with a major teratogenic risk when used during the first trimester of pregnancy; caution, however, is still warranted.

Therapeutic Uses. Proton pump inhibitors are used principally to promote healing of gastric and duodenal ulcers and to treat *g*astric *e*sophageal *r*eflux *d*isease (GERD) that is either complicated or unresponsive to treatment with H_2-receptor antagonists (*see* below). Proton pump inhibitors also are the mainstay in the treatment of Zollinger-Ellison syndrome. Therapeutic applications of proton pump inhibitors are further discussed later in this chapter, under "Specific Acid-Peptic Disorders and Therapeutic Strategies."

HISTAMINE H_2-RECEPTOR ANTAGONISTS

The description of selective histamine H_2-receptor blockade by Black in 1970 was a landmark in the history of pharmacology and set the stage for the modern approach to the treatment of acid-peptic disease, which until then had relied almost entirely on acid neutralization in the lumen of the stomach (*see* Black, 1993; Feldman and Burton, 1990a,b). Equally impressive has been the safety record of H_2-receptor antagonists, a feature that eventually led to their availability without a prescription. Increasingly, however, these agents are being replaced by the more efficacious albeit more expensive proton pump inhibitors.

Chemistry, Mechanism of Action, and Pharmacological Properties. Four different H_2-receptor antagonists are currently on the market in the United States: *cimetidine* (TAGAMET), *ranitidine* (ZANTAC), *famotidine* (PEPCID), and *nizatidine* (AXID) (Figure 37–3). Their different chemical structures do not alter the drugs' clinical efficacies as much as they determine interactions with other drugs and change the side-effect profiles. H_2-receptor antagonists inhibit acid production by reversibly competing with histamine for binding to H_2 receptors on the basolateral membrane of parietal cells.

The most prominent effects of H_2-receptor antagonists are on basal acid secretion; less profound but still significant is suppression of stimulated (feeding, gastrin, hypoglycemia, or vagal stimulation) acid production. These agents thus are particularly effective in suppressing

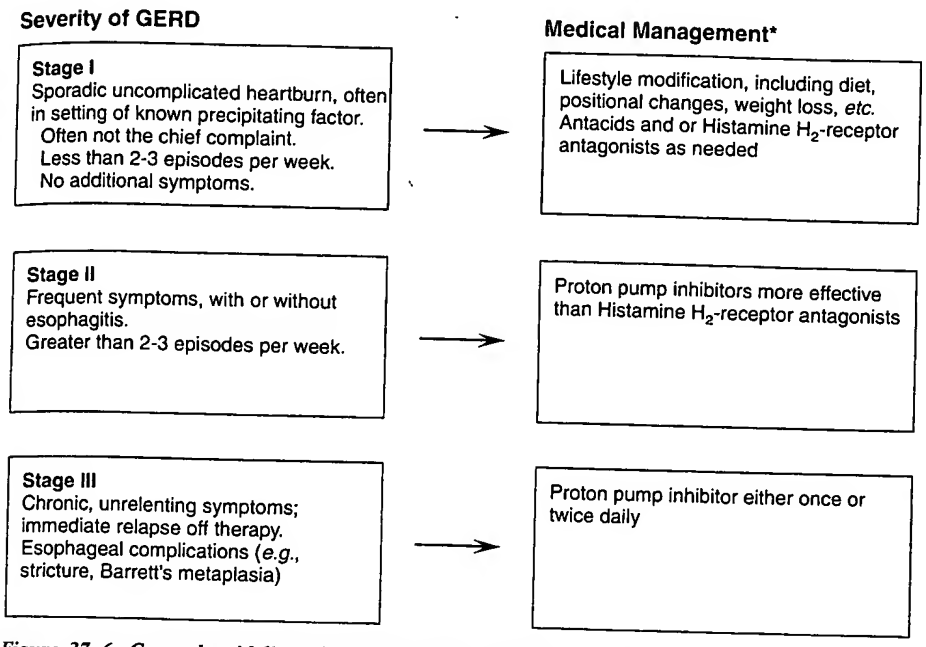


Figure 37–6. General guidelines for medical management of gastroesophageal reflux disease (GERD).

*Only acid production–suppressing and acid-neutralizing medication included. *(Adapted from Wolfe and Sachs, 2000, with permission.)*

decades; so has the incidence of esophageal adenocarcinoma, particularly in white males. An association has been suggested between GERD symptoms and the incidence of esophageal adenocarcinoma (Lagergren *et al.*, 1999). An increasing number of reports also link GERD and tracheopulmonary symptoms such as chronic laryngitis and asthma, although a cause-and-effect relationship is still somewhat controversial. Finally, it should be borne in mind that GERD is a chronic disorder that requires long-term therapy (DeVault, 1999).

Although the pathophysiology of GERD has more to do with a disturbance of gastrointestinal motility (*see* Chapter 38), most of the symptoms are due to the injurious effects of the acid-peptic refluxate on the esophageal epithelium. This provides the rationale for the current pharmacotherapeutic approach to treating this syndrome, which is based on suppression of gastric acid. Traditional prokinetic agents have been of limited efficacy, but more specific agents currently are being developed and may hold greater promise (Chapter 38).

Treatment of Acute GERD Symptoms. The goals of GERD therapy are complete resolution of symptoms and healing of esophagitis. Proton pump inhibitors are clearly more effective than H_2-receptor antagonists in achieving both of these goals. Healing rates after 4 weeks and 8 weeks of therapy with proton pump inhibitors are around 80% and 90%, respectively; healing rates with H_2-receptor antagonists are 50% and 75%. Indeed, proton pump inhibitors are so effective that their empirical use has been advocated as a therapeutic trial in patients in whom GERD is suspected to play a role in the pathogenesis of symptoms. The "omeprazole test" involves giving omeprazole for a period of 12 weeks to patients with noncardiac chest pain. Expensive diagnostic tests are instituted only if such a trial fails (Fass *et al.*, 1998). Because of the wide clinical spectrum associated with GERD, the therapeutic approach is best tailored to the level of severity in the individual patient (Figure 37–6). In general, the optimal dose for each individual patient should be determined based upon symptom control. Only in patients with complicated GERD and/or Barrett's esophagus is documentation of complete acid control with 24-hour pH monitoring indicated.

Regimens for the treatment of GERD with proton pump inhibitors and histamine H_2-receptor antagonists are listed in Table 37–4. Although some patients with mild GERD symptoms may be managed by nocturnal doses of H_2-receptor antagonists, dosing two or more times a day generally is required. In patients with severe symptoms or extraintestinal manifestations of GERD, twice-daily dosing with a proton pump inhibitor may be needed. It has been shown, though, that nocturnal acid breakthrough can occur even with twice-daily proton pump inhibitor dosing in healthy subjects and that this can be controlled by the addition of an H_2-receptor antagonist at bedtime (Peghini *et al.*, 1998). The clinical importance of this finding for GERD patients with poorly responsive symptoms to standard dosing of proton pump inhibitors needs further evaluation.

A popular approach to GERD therapy, encouraged by managed-care companies, consists of a "step-up" regimen, beginning with an H_2-receptor antagonist and only progressing to one of the proton pump inhibitors if symptoms fail to respond. While theoretically appealing, this approach carries the risk of